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Clinical and Angiographic Outcomes With Sirolimus-Eluting Stents in Total Coronary Occlusions

The ACROSS/TOSCA-4 (Approaches to Chronic Occlusions With Sirolimus-Eluting Stents/Total Occlusion Study of Coronary Arteries-4) Trial

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Objectives We sought to examine angiographic and clinical outcomes with sirolimus-eluting stents (SES) in total coronary occlusion (TCO) revascularization.

Background Despite evaluation of drug-eluting stents beyond approved indications, few studies have evaluated their clinical benefit in TCO revascularization.

Methods Among 15 centers in North America, 200 consecutive TCO patients (78.8% >6 weeks TCO age) were enrolled for treatment with SES. The primary end point was 6-month angiographic binary restenosis within the treated segment.

Results Patient characteristics included: diabetes, 24.5%; prior infarction, 33.5%; and stent length, 45.9 mm median (quartile 1, 30.2 mm; quartile 2, 62.1 mm). A total of 199 patients (99.5%) were treated with SES, and procedural success was 98.0%. The 6-month binary restenosis rates were 9.5% in-stent, 12.4% in-segment, and 22.6% in-"working length" representing the entire treatment segment. Rates of 1-year target lesion revascularization, myocardial infarction, and target vessel failure were 9.8%, 1.0%, and 10.9%, respectively. Stent thrombosis occurred in 2 patients (1.0%). Using logistic regression modeling with propensity score adjustment, the absolute reduction in binary restenosis with SES compared with a historical bare-metal stent control was 37.7% (95% confidence interval [CI]: 27.2% to 48.3%, $p < 0.001$; odds ratio: 0.17, 95% CI: 0.09 to 0.30, $p < 0.0001$). Among 32 patients (16%) identified with stent fracture, target lesion revascularization was more common than patients without fracture (25.0% vs. 6.7%, $p = 0.005$).

Conclusions Despite greater lesion complexity than prior TCO trials, percutaneous revascularization with SES appears safe and results in substantial reductions in angiographic restenosis and failed patency and a low rate of repeat revascularization. These findings support the use of SES in TCO revascularization. (The ACROSS/TOSCA Trial; NCT00378612). (J Am Coll Cardiol Intv 2009;2:97–106)

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Compared with bare-metal stents, drug-eluting stents (DES) result in large and important reductions in angiographic restenosis and the need for repeat revascularization when tested in restricted clinical trial cohorts. Beyond the context of randomized trials with more restrictive enrollment criteria, observational studies evaluating outcomes in less controlled and more complex cohorts have allowed clinicians to safely and routinely extend the use of DES to a broader percutaneous coronary intervention population.

Nonacute and chronic total coronary occlusions (TCOs) remain a formidable challenge and unresolved dilemma in the practice of interventional cardiology. In particular, percutaneous TCO revascularization is plagued by both primary and late failure. High rates of target lesion failure after use of balloon angioplasty or bare-metal stents in this lesion subset has been associated with impairment in left ventricular function, recurrent angina, repeat target vessel revascularization, and the need for bypass surgery (1). The potential for DES to improve long-term vessel patency after TCO recanalization is suggested by both the observed efficacy of DES in less complex lesion subsets and by the historic limitations of bare-metal stents in TCO revascularization.

Abbreviations and Acronyms

DES = drug-eluting stent(s)

SES = sirolimus-eluting stent(s)

TCO = total coronary occlusion(s)

TLR = target lesion revascularization

Preliminary reports describing DES efficacy in TCOs are promising, with comparatively low rates of restenosis and reocclusion (2–7). However, reports describing rigorously obtained clinical and angiographic outcomes after DES use in minimally selected TCOs are lacking. Accordingly, we performed the ACROSS/TOSCA-4 (Approaches to Chronic Occlusions with Sirolimus-Eluting Stents/Total Occlusion Study of Coronary Arteries-4) study, a multicenter, nonrandomized prospective trial examining the safety and efficacy of sirolimus-eluting stents (SES) in percutaneous TCO revascularization.

Methods

Trial overview and study population. The ACROSS/TOSCA-4 trial was an investigator-initiated, prospective, nonrandomized multicenter trial evaluating the safety and efficacy of treatment with SES in patients undergoing elective percutaneous TCO revascularization at 15 hospitals in North America (Online Appendix). The study was approved by the institutional review board at each site. Eligible patients signed written informed consent before the interventional procedure. To enable comparison with a historical control group treated with bare-metal stents, clinical and angiographic inclusion and exclusion criteria were modeled after those employed in the TOSCA-1 (Total Occlusion Study of Canada-1) trial (8). Eligible patients were age 18 years or older undergoing clinically driven nonemergent percutaneous recanalization of a de novo occlusive coronary lesion exhibiting Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1 and judged able to accommodate an angioplasty balloon of ≥3.0-mm diameter. Consenting patients were considered enrolled upon successful crossing of the occluded segment with any coronary guidewire and confirmation of guidewire placement in the distal true lumen. Principal angiographic exclusion criteria were in-stent total occlusions and excessive vessel angulation deemed by the operator likely to prohibit stent delivery. There were no restrictions regarding lesion length. Clinical exclusion criteria were recent (<72 h) myocardial infarction, prior stent placement within the target vessel or any other vessel within 90 days of the index procedure, or any general contraindication to the revascularization procedure and routine pharmacologic therapies.

Interventional procedure and adjunctive drug therapies. Patients were treated with the sirolimus-eluting Cypher coronary stent (Cordis Corporation, Warren, New Jersey), available in diameters ranging from 2.5 to 3.5 mm and in lengths from 8 to 33 mm. Placement of up to 2 33-mm SES was permitted per protocol except in instances of insufficient lesion coverage or as a "bailout" procedure for dissection or thrombus. All lesions were pre-dilated with balloon angioplasty, and the protocol specified that stent length should be ≥4 mm longer than the lesion for adequate coverage. Treatment with additional device therapies (e.g., atherectomy) was not permitted. Stents were expanded to achieve <10% residual stenosis by visual estimate throughout the treated segment with use of supplemental post-deployment balloon angioplasty left to operator discretion.

Prior to revascularization, all patients received treatment with aspirin (325 mg/day) and clopidogrel (75 mg/day) for at least 48 h, followed by dual antiplatelet therapy for a minimum of 3 months after the procedure and indefinite aspirin therapy. In those patients not receiving at least 48 h of dual antiplatelet therapy before the procedure, a loading dose of clopidogrel (300 to 600 mg) was given immediately before or during the procedure. Procedural antithrombin and intravenous glycoprotein IIb/IIIa inhibitor therapies were selected at the treating physician's discretion but were administered according to protocol-recommended algorithms.

Clinical events were assessed during hospitalization and at 30 days, 6 months, and planned annually for 5 years after the index procedure. All patients were scheduled to undergo follow-up angiography at 6 months or sooner if the patient developed angina or objective evidence of target vessel ischemia.

Data management and core laboratories. All data were submitted to a central data coordinating facility (Duke Clinical Research Institute, Durham, North Carolina). Coronary angiograms performed at baseline and at follow-up were reviewed by the independent angiographic

core laboratory employed for TOSCA-1 (Cardiovascular Imaging Research Core Laboratory, University of British Columbia, Vancouver, British Columbia) and analyzed using the same methods (8). Standard image acquisition was performed using 2 or more angiographic projections of the occluded segment before and after stent placement. Compulsory angiography was planned 180 ± 30 days after the procedure using identical angiographic projections. Quantitative analysis of lumen dimensions was performed using the Discovery system (Quinton, Bothell, Washington). Treated segment, or "working" length, represented the contiguous length of the target vessel occlusion exposed to balloon inflation and was measured using images recorded throughout the procedure. Side branches, bends, and other fixed features were used to provide points of reference. A 5- to 10-mm angiographically disease-free segment of reference diameter proximal and distal to the treated segment was used to calculate the average reference vessel diameter after stent implantation and at follow-up. However, only the proximal disease-free segment was used to calculate the reference diameter at baseline in the context of total occlusions or for other instances in which the distal reference vessel was poorly visualized. Moreover, to maintain consistency with comparison to the TOSCA-1 binary restenosis rate in the treated segment, diameter stenosis was calculated using a proximal reference diameter. Quantitative analysis was performed to evaluate the in-stent region (bordered by the stent margins) and the peristent, or "in-segment" region (in-stent region plus 5-mm margins proximal and distal to the stent). For the latter 2 measures, an average of both the proximal and distal reference diameters were applied to calculate diameter stenosis.

Study end points and definitions. The primary end point, angiographic restenosis within the entire treated segment, was examined by quantitative coronary angiography at 6-month follow-up. The treated segment was defined as the length of contiguous target segment exposed to balloon angioplasty pre-dilation, irrespective of stent placement. Angiographic binary restenosis was defined as a stenosis equal to or greater than 50% of the lumen diameter of the target lesion (determined by the core angiographic laboratory). Secondary angiographic end points included in-segment late loss, failed patency (TIMI flow grade <3 and ≥70% in-segment diameter stenosis), reocclusion (TIMI flow grade 0 or 1 at final angiography), and in-stent restenosis.

Pre-specified clinical safety and efficacy end points included major adverse cardiac events (all-cause death, myocardial infarction, and clinically driven target lesion revascularization [TLR]) and its components reported at 30 days 6 months and at 1 year stent thrombosis (per protocol and expanded definition criteria [9]), clinically driven target vessel revascularization at 6 months and target vessel failure (cardiovascular death, myocardial infarction, and clinically driven target vessel revascularization) at 6 months. Device success was defined as a <50% diameter stenosis of the target lesion upon completion of the index procedure as determined by the core angiographic laboratory. Procedural success was defined as device success and no in-hospital major adverse cardiac events. Myocardial infarction was defined as a creatine kinase elevation ≥2 times above the upper limit of normal with any associated elevation in the creatine kinase myocardial band or the development of new pathologic Q waves in 2 contiguous electrocardiographic leads. Clinically driven revascularization was identified as any repeat revascularization of the target lesion or target vessel associated with either: 1) ischemic symptoms and/or an abnormal functional study and a ≥50% coronary stenosis by quantitative angiography; or 2) any revascularization of a ≥70% diameter stenosis. All primary and secondary clinical end points were adjudicated by an independent clinical events committee.

Stent fracture was defined as an acquired discontinuity of stent architecture within the originally stented segment. For consistency, and in view of the potential importance of this phenomenon with respect to late clinical events, all cineangiograms were reviewed for this occurrence. Consensus of 2 independent reviewers was required. Discordant results were resolved by consensus. This method differed from the TOSCA-1 trial, in which stent fracture was not prospectively examined.

Statistical methods. The primary hypothesis of this study was that compared with patients treated with bare-metal stents in the TOSCA-1 study (N = 202), patients treated with SES would show a ≥50% relative reduction in the 6-month occurrence of the primary end point of angiographic binary restenosis within the treated segment of the target vessel. Accordingly, enrollment criteria and trial methodology were modeled after the TOSCA-1 trial for comparability. Under this assumption, with a sample size of 200 patients, the study had more than 95% statistical power to determine statistical superiority of the primary end point at a 1-sided 0.025 level of statistical significance.

To compare angiographic restenosis between patients included in the current and comparator trials, 2 prespecified analytical methods were applied. In the primary model (10), outcomes were compared using an inverse probability weighted analysis. This analysis used a propensity score (11) that was calculated using 5 clinical and angiographic variables identified as predictors of angiographic restenosis in prior randomized trials comparing bare-metal stents and DES (diabetes, reference vessel diameter, lesion length, age, current smoker status). A second analysis was completed using a propensity score constructed with 3 covariates (diabetes, reference vessel diameter, lesion length). In the secondary model, logistic regression was applied. Given the nonrandomized nature of this comparison, propensity score for study selection was calculated and

used as an adjustment factor in the multivariable analysis, which also included other pre-specified clinical and angiographic predictors of restenosis (e.g., diabetes, lesion length, reference vessel diameter). Sensitivity analysis was applied to assess the influence of unmeasured confounders (12).

Patients were analyzed for all primary and secondary efficacy and safety end points based on the intent-to-treat principle. Patients who did not return for the 6-month angiographic follow-up had a restenosis value estimated using multiple imputations by study membership via the Markov Chain Monte-Carlo method using PROC MI in SAS software (SAS Institute Inc., Cary, North Carolina).

Baseline characteristics of study patients were summarized in terms of frequencies and percentages for categorical variables and by medians, 25th and 75th distribution percentiles for continuous variables. Categorical variables were compared by chi-square test and Fisher exact test when cell sizes were <5. Continuous variables were compared by the 2-sample *t* test. A p value of 0.05 was established as the level of statistical significance for all tests. Clinical and angiographic predictors of restenosis were identified using multivariable logistic regression. All analyses were performed using SAS software (version 8.2, SAS Institute).

Results

Patient characteristics. Among 200 patients enrolled, all patients except 1 received treatment with SES, and 1 SES patient received additional treatment with a bare-metal stent. Overall, the median age was 60.3 years, one-third had a history of myocardial infarction, and 24.5% had diabetes mellitus (Table 1). Most (78.8%) were characterized as having a total occlusion exceeding 6 weeks of age. Nearly half of the target lesions were located in the right coronary artery, and most were proximal.

Consistent with more diffuse disease associated with coronary total occlusions, the median (Q1, Q3) treated, or working length segment, as an indirect measure of TCO lesion length was 49.6 (33.4, 64.5) mm. Side branch occlusions involving the TCO were present in 9.7% of lesions.

Procedural and in-hospital outcomes. The median stent length per target lesion was 45.9 (30.2, 62.1) mm. Three-quarters of patients received at least 2 stents and 37% of patients received 3 or more stents (Table 2). Procedural success was achieved in 98% of patients (Table 2). Procedural failure (hierarchal) was due to in-hospital adverse events (n = 3), failure to achieve <50% residual stenosis (n = 2), and/or inability to deliver only the assigned study device (n = 1). Two cases of early repeat revascularization were performed exclusively for failure to achieve initial patency in the target vessel.

Angiographic and clinical outcomes. Qualifying follow-up angiography was performed and suitable for core laboratory analysis in 170 (85.0%) patients. Clinical follow-up was available in 196 patients (98.0%) at 180 days and 193 patients (96.5%) at 365 days. The primary end point, restenosis within the entire treated segment, occurred in 22.6% (Table 3); rates of in-stent and segment restenosis were 9.5% and 12.4%, respectively. Among patients with angiographic in-stent restenosis, patterns of restenosis were characterized as focal (10 patients, 62.5%), diffuse intrastent (n = 4, 25.0%), diffuse proliferative (none), and total occlusion (n = 2, 12.5%). Rates of restenosis were higher among patients with diabetes, longer durations of vessel occlusion, and those with longer stent lengths and overlapping stents (Fig. 1). Median late lumen loss was 0.10 (−0.57, 0.15)-mm in-stent and −0.11 (−0.22, 0.37)-mm in-segment. Failed patency at 6 months, defined as ≥70% stenosis with TIMI flow grade <3 at angiographic follow-up, occurred in 2.9% of patients, all of whom were identified with TIMI flow grade 0 (n = 2) or 1 (n = 3).

Compared with a historical control of patients treated with bare-metal stents for TCO revascularization in the

Table 1. Baseline Patient Clinical and Angiographic Characteristics

	Sirolimus-Stent Group (N = 200)
Clinical characteristics	
Age, yrs	60.3 (54.8,69.7) (200)
Male, %	80.0 (160/200)
Diabetes mellitus, %	24.5 (49/200)
Hypertension, %	69.5 (139/200)
Age of occlusion >6 weeks	78.8 (119/151)
History of smoking, %	67.5 (135/200)
Hyperlipidemia, %	86.0 (172/200)
Prior myocardial infarction, %	33.5 (67/200)
Angina class III/IV, %	29.5 (59/200)
Heart failure class III/IV, %	4.5 (9/200)
Prior percutaneous revascularization, %	32.5 (65/200)
Prior coronary bypass surgery, %	8.5 (17/200)
Angiographic characteristics	
Target vessel, %	
Left anterior descending artery	29.5 (59/200)
Right coronary artery	49.0 (98/200)
Left circumflex artery	21.5 (43/200)
TIMI flow grade 0/1, %	95.5 (191/200)
Moderate/severe calcification, %	46.4 (92/198)
Side branch occlusion, %	9.7 (3/31)
Reference vessel diameter, mm	2.93 (2.59, 3.30) (177)
Treated segment length, mm	49.60 (33.40, 64.50) (197)
Lesion location, %	
Ostial/proximal	55.5 (111/200)
Mid	33.5 (67/200)
Distal	11.0 (22/200)

Values expressed as n (%) or median (Q1, Q3) (n). Angina and heart failure severity according to Canadian Cardiovascular Society and New York Heart Association classifications, respectively.
TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Procedural Angiographic Results and In-Hospital Clinical Events

	Sirolimus-Stent Group (N = 200)
Procedural characteristics	
Number of stents	2.0 (1.5, 3.0) (196)
Stent length, mm	45.9 (30.2, 62.1) (199)
Stent diameter, mm	3.00 (2.75, 3.09) (196)
Inflation pressure, atm	16.0 (14.0, 18.0) (198)
≥2 stents implanted, %	75.0 (147/196)
Overlapping stents, %	92.0 (137/149)
Minimal luminal diameter, mm	
Before procedure	
In-lesion	0 (0, 0) (198)
After procedure	
In-stent	2.43 (2.19, 2.75) (196)
In-segment	1.93 (1.53, 2.31) (196)
Treated segment	2.32 (1.96, 2.61) (197)
Diameter stenosis, %	
Before procedure	
In-lesion	100 (100, 100) (200)
After procedure	
In-stent	9.0 (0, 17.0) (196)
In-segment	27 (19.0, 38.5) (196)
Treated segment	14.0 (4.5, 24.0) (196)
Device success, %	99.0 (198/200)
Procedural success, %	98.0 (195/199)
In-hospital outcomes	
Death, %	0 (0/199)
Myocardial infarction, %	1.0 (2/199)
Q-wave, %	0 (0/199)
Non–Q-wave, %	1.0 (2/199)
Stent thrombosis, %	0 (0/199)
Target lesion revascularization, %	1.0 (2/199)
Nontarget lesion related target vessel revascularization, %	0 (0/199)
Major adverse cardiac events, %	1.5 (3/199)

Values expressed as n (%) or median (Q1, Q3) (n).

TOSCA-1 trial, patients treated with SES in the present study had significantly smaller target vessel diameters, older total occlusions, longer lesions and stent lengths, and a higher incidence of diabetes mellitus (Table 4). In univariable analysis, total stent length per millimeter ($p = 0.008$), current smoking ($p = 0.01$), diabetes ($p = 0.002$), and number of stents implanted ($p = 0.046$) were significant predictors of in-stent angiographic restenosis. Despite greater lesion complexity and clinical characteristics associated with angiographic restenosis, treatment with SES was associated with an unadjusted 59% relative reduction in the angiographic primary end point (6-month treated lesion length restenosis rates: 55.2% TOSCA-1 trial vs. 22.6% ACROSS/TOSCA-4). The adjusted absolute reduction in restenosis rates was 37.7% (95% confidence interval [CI]: 27.2 to 48.3, $p < 0.001$) when adjusting for the 5-variable propensity score, and 36.4% (95% CI: 26.1 to 46.8, $p < 0.001$) when adjusting for the 3-variable propensity score. Using logistic regression adjusted for the 5-variable propensity score, the relative reduction in odds of restenosis with SES was 83% (odds ratio [OR]: 0.17, 95% CI: 0.09 to 0.30; $p < 0.0001$) and similarly 84% (OR: 0.16, 95% CI: 0.09 to 0.28; $p < 0.0001$) in the 3-variable model. Aside from the reduction in angiographic restenosis, the end point of failed patency was also significantly reduced among patients treated with SES (10.9% TOSCA-1 trial vs. 2.9% ACROSS/TOSCA-4, unadjusted $p = 0.005$).

At 1 year, there were no deaths and no episodes of out-of-hospital myocardial infarction (Table 3). Major adverse cardiac events were infrequent, occurring in 20 (10.3%) patients most commonly due to repeat revascularization. Similarly, the rate of target vessel failure was 10.9%. At 6 months, 12 (6.0%) patients underwent repeat TLR, accounting for all repeat target vessel revascularization

Table 3. 6-Month Angiographic and 1-Year Clinical Outcomes

	Sirolimus-Stent Group (N = 200)
Quantitative angiography	
Late lumen loss, mm	
In-stent	0.10 (–0.57, 0.15) (146)
In-segment	–0.11 (–0.22, 0.37) (146)
Treated segment	0.04 (–0.49, 0.23) (146)
Minimal luminal diameter, mm	
In-stent	2.27 (1.89, 2.69) (147)
In-segment	2.02 (1.65, 2.37) (147)
Treated segment	2.13 (1.80, 2.56) (146)
Diameter stenosis, %	
In-stent	18.0 (9.0, 33.5) (168)
In-segment	30.5 (19.0, 42.0) (169)
Treated segment	32.0 (21.0,47.0) (168)
Binary restenosis, %	
In-stent	9.5 (16/169)
In-segment	12.4 (21/169)
Treated segment	22.6 (38/168)
Failed patency, %	5/168 (2.9%)
Clinical events	
Death, %	0 (0/193)
Myocardial infarction, %	1.0 (2/193)
Q-wave, %	0 (0/193)
Non–Q-wave, %	1.0 (2/193)
Stent thrombosis, %	1.0 (2/193)
Target lesion revascularization, %	9.8 (19/193)
Percutaneous	8.8 (17/193)
Surgical	1.0 (2/193)
Target vessel revascularization–not involving target lesion, %	1.6 (3/193)
Target vessel failure, %	10.9 (21/193)
Major adverse cardiac events, %	10.3 (20/193)

Values expressed as n (%) or mean (± SD).

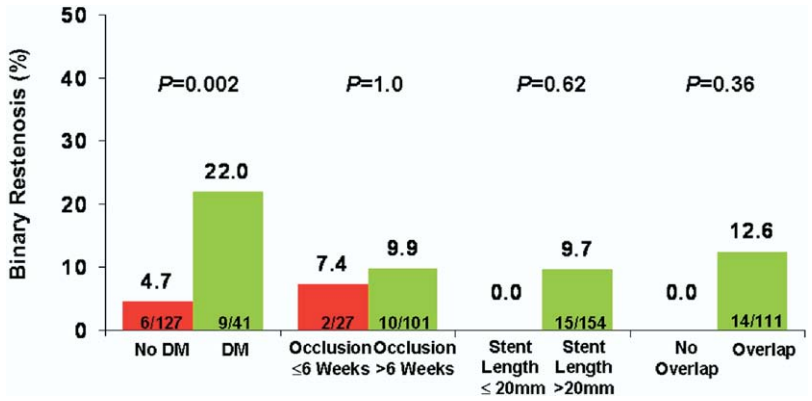

Figure 1. In-Stent Angiographic Binary Restenosis Among Selected Patient Subgroups

Rates of 6-month angiographic in-stent binary restenosis for selected patient subgroups. Rates of restenosis were higher among patients with diabetes, longer durations of vessel occlusion, and those with longer stent lengths and overlapping stents. DM = diabetes mellitus.

procedures during that period. By 1 year, TLR occurred in an additional 7 patients, contributing to an overall rate of 9.8%.

Adherence to dual antiplatelet therapy at 6- and 12-month follow-up was documented for 93.7% (177 of 193) and 83.1% (157 of 189) patients, respectively. By 1 year, stent thrombosis per protocol angiographic definition was adjudicated for 2 patients. There were no probable or possible stent thrombosis events (9). In the first episode, nonocclusive thrombus was identified during protocol-mandated angiographic follow-up 115 days after the index revascularization and resulted in repeat percutaneous revascularization. In the second event, thrombus was identified in a side branch related to the target segment immediately after the index procedure. At 236 days, the patient underwent percutaneous revascularization in non-target vessel–related territories. Angiography showed persistence of side branch thrombus and a patent target vessel stent in an asymptomatic patient. Neither event was associated with ischemic symptoms or abnormal biomarker findings related to the target vessel.

Coronary angiograms were independently reviewed by 2 examiners for stent fracture and adjudicated by consensus. Among 32 patients (16%) identified with definite or probable stent fracture (56 events; 44 definite, 12 probable) during angiographic follow-up, in-stent angiographic restenosis occurred in 5 patients (Table 5). Characteristics common to patients identified with stent fracture included right coronary artery location (84%), significant (>45°) vessel angulation (23%), and/or stent placement in regions of extreme dynamic motion (14%). Compared with patients not observed with stent fracture, those identified with stent fracture had significantly greater total stent length. Although infrequent, rates of in-stent and -segment binary restenosis were approximately 2-fold higher for patients with stent fracture compared with non-stent fracture patients. However, restenosis at the site of stent fracture occurred in only 2 of the 5 patients, although 1 patient

Table 4. Comparison of Selected Patient Characteristics Between ACROSS/TOSCA-4 and TOSCA-1 Trial Populations

	ACROSS/TOSCA-4 (N = 200)	TOSCA-1 (N = 202)	p Value
Age, yrs	60.3 (54.8, 69.7) (200)	57.7 (50.0, 65.7) (202)	<0.001
Age of occlusion >6 weeks, %	78.8 (119/151)	36.6 (48/131)	<0.001
Reference vessel diameter, mm	2.93 (2.59, 3.30) (177)	3.31 (2.93, 3.71) (201)	<0.001
Current smoker, %	17.5 (35/200)	17.8 (36/202)	0.93
Diabetes, %	24.5 (49/200)	14.9 (30/202)	0.02
Male, %	80.0 (160/200)	83.7 (169/202)	0.34
Hypertension, %	69.5 (139/200)	34.7 (70/202)	<0.001
Target vessel: left anterior descending artery, %	29.5 (59/200)	38.6 (78/202)	0.05
Stent length, mm	45.8 (30.2, 62.1) (198)	28.0 (15.0, 42.0) (193)	<0.001
Treated segment length, mm	49.6 (33.4, 64.5) (197)	31.4 (20.0, 46.5) (202)	<0.001

Values expressed as n (%) or median (Q1, Q3) (n).

Table 5. Comparison of 6-Month Angiographic and 1-Year Clinical Characteristics Between Patients With and Without Stent Fracture

	Stent Fracture (n = 32)	Nonstent Fracture (n = 168)	p Value
Stent length, mm	65.5 (49.7, 73.6)	41.9 (28.8, 57.0)	<0.001
Overlapping stents, %	100 (30/30)	89.9 (107/119)	0.06
Procedural success, %	100.00 (32/32)	97.6 (163/167)	1.00
Target lesion revascularization, %	25.0 (8/32)	6.7 (11/162)	0.005
Major adverse cardiac events, %	25.0 (8/32)	7.4 (12/161)	0.007
Stent thrombosis, %	3.2 (1/31)	0.6 (1/162)	0.30
Binary restenosis, %			
In-segment	25.0 (8/32)	9.5 (13/137)	0.017
In-stent	15.6 (5/32)	8.0 (11/137)	0.17

Values expressed as n (%) or median (Q1, Q3) (n).

experienced restenosis at 2 separate fracture sites. Among all cases of stent fracture, 41% were localized to the body of the stent, and 59% were identified in or immediately adjacent to the segment of overlapping stents. There was no associated aneurysm formation. At 1-year follow-up, TLR was significantly more common in patients identified with stent fracture (25.0% vs. 6.7%, p = 0.005) (Table 5), yet repeat revascularization at the site of fracture occurred only in 3 of 8 patients.

Discussion

In this prospective evaluation of the clinical efficacy, safety and angiographic outcomes among patients treated with DES in complex TCO revascularization, percutaneous revascularization with SES resulted in substantial reductions in angiographic restenosis and failed patency and a low rate of repeat revascularization. Treatment with SES led to these results despite the presence of higher-risk patients and more complex lesion characteristics compared with a historical bare-metal stent control. These findings further support the use of SES in TCO revascularization.

Unlike the widespread evaluation of DES beyond approved patient and lesion indications, until recently, few investigations have been performed to support the clinical benefit of DES in total occlusion revascularization. In particular, our understanding of procedural and mid-term safety and efficacy of DES after TCO revascularization has been limited by the routine exclusion or underrepresentation of such patients in most major interventional cardiology clinical trials. Despite greater lesion complexity than in prior TCO trials, treatment with SES was associated with a significant ~37% absolute rate reduction and ~85% relative reduction in the odds of angiographic restenosis compared with patients treated with conventional bare-metal stents in a similar clinical setting and after comparison adjusted for propensity scores for clinical and angiographic characteristics. Considering, for example, that the median-treated lesion length and stent length in the current study were 49.6 mm and 45.9 mm, respectively, patients included in this trial represent one of the most challenging lesion subsets evaluated with DES treatment. However, despite more complex lesion morphology in contrast to patients treated with bare-metal stents (e.g., older total occlusion duration, smaller reference vessel caliber, longer lesion and stent length) and a higher frequency of diabetes—characteristics predictive of angiographic and clinical restenosis—percutaneous revascularization with SES resulted in very favorable rates of in-stent binary restenosis (9.5%) and 1-year TLR (9.8%). Moreover, these results were observed in the context of a relatively high rate of protocol-specified follow-up angiography. These findings are similar to the smaller, randomized PRISON II (Primary Stenting of Totally Occluded Native Coronary Arteries II) study (SES treatment, N = 100), in which treatment with SES resulted in a 6-month angiographic binary restenosis rate of 7.0%, a 73% relative reduction in in-segment restenosis compared with bare-metal stents and a 5.0% incidence of repeat TLR (2). In the present study, however, the slightly higher 1-year rate of repeat revascularization is likely attributed to substantially greater patient clinical and lesion complexity (e.g., 2.5-fold increase in diabetes, 3-fold increase in lesion length, 1.5-fold increase in average number of stents).

Compared with prior retrospective, observational studies evaluating DES treatment in patient subgroups of a larger study population and with more variable angiographic surveillance (3–7), methods in the present study also differed by the assessment of lesion length treated in the occluded segment. In particular, evaluation of restenosis according to the entire treated segment, in addition to more contemporary measures within the stent and peristent regions, not only reflects a revascularization technique that is unique to TCO revascularization but may also be more clinically relevant. Because assessment of disease adjacent to the occluded segment is not routinely visible, and the entire segment pre-dilated with balloon angioplasty is not always

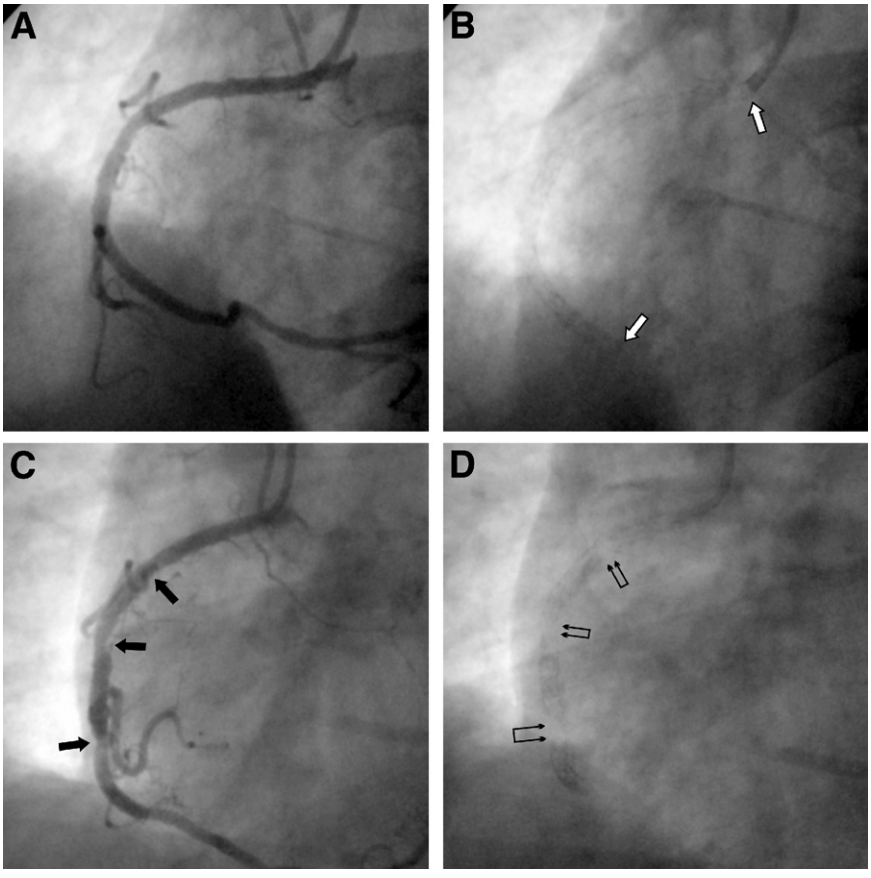

Figure 2. Coronary Stent Fracture Following TCO Revascularization With Sirolimus-Eluting Stents

Transverse, disarticulated stent fractures in the right coronary artery identified at 6-month angiography **(bracketed arrows, D)** with insignificant focal restenosis **(closed arrows, C)** compared with baseline imaging following total coronary occlusion (TCO) revascularization with 4 contiguous, overlapping stents **(white arrows, A, B)**.

treated with stent placement once antegrade flow is restored and visibility improved, assessment of outcomes within the treated segment may more accurately reflect outcomes after TCO revascularization than those limited to the in-stent segment. Perhaps due to an angiographically acceptable result with balloon angioplasty alone, and/or a reluctance to perform more extensive stenting, a longer disease segment was treated with angioplasty than with stenting so that when restenosis did occur, it was considerably more common in regions beyond the stent margins. Such findings have implications in routine clinical practice, suggesting that more extensive atherosclerosis associated with total occlusions may be better treated with SES rather than with angioplasty alone or bare-metal stents (13).

An additional study method unique to this trial was the prospective assessment for coronary stent fracture, which was characterized after adjudicated review of follow-up angiograms as definite or probable for 32 patients (Fig. 2). Although more commonly identified after lower limb revascularization with stents, coronary stent fracture is a more recent observation for which the cause and outcome are not well understood. Consistent with a prior descriptive study, stent fracture is most commonly associated with increasing stent length and in coronary segments identified with significant angulation or dynamic flexure before stenting (e.g., right coronary artery) (14). No stent fractures were identified in the TOSCA-1 trial, in which patients were treated with shorter (e.g., 15-mm length) stents, leading to significantly shorter total stent length. Thus, the current results may reflect an interaction between longer, overlapping stent segments and more regions of dynamic flexure, in comparison with TOSCA-1. In accord with 6-month rates of restenosis that were approximately twice as common when compared with patients without fracture, the 1-year repeat revascularization was significantly higher among patients with stent fracture. However, it is difficult to fully separate the role of stent length from that of stent fracture in the genesis of restenosis in this study because there was a

significantly longer stent length in the fracture group (66 mm vs. 42 mm), and yet restenosis at the fracture site was identified in only 2 patients.

Study limitations. In the absence of randomization, a limitation to this analysis is that despite the use of a propensity score methodology, the possibility that measured or unmeasured confounders may have affected the results of the study cannot be excluded. However, this issue has been addressed by adjusting for pre-specified known predictors of angiographic restenosis in propensity score analyses, and performing sensitivity analyses to evaluate the influence of possible unmeasured confounders on the study results. All analyses showed consistent evidence of superiority of SES compared with bare-metal stents in the TOSCA-1 study. In addition, although analysis of angiographic and clinical outcomes was similar between trials, the primary end points differed between the current study (angiographic binary restenosis) and the TOSCA-1 trial (failed patency). However, failure of sustained patency, a secondary end point in this trial, was also significantly reduced with SES compared with the bare-metal stent control. Also, in comparison with some prior studies of occluded arteries, not all TCOs were estimated as "chronic" in age. To our knowledge, the estimated age of a TCO has historically been related to technical success of recanalization rather than later term angiographic or clinical outcomes. Nevertheless, approximately 20% of patients in the present study had a TCO age estimated <6 weeks, although this proportion is considerably lower than the TOSCA-1 trial and more recent total occlusion studies (2,8). Finally, an association between stent fracture and clinical outcome should be considered hypothesis generating given that the temporal association between a fracture and an adverse event was not established for all patients. Diagnostic accuracy for stent fracture may also vary according to method (e.g., fluoroscopy, intravascular ultrasound), and limiting analysis to fluoroscopy alone may have underestimated its incidence. Without an established method to identify this finding, we performed independent reviews by 2 examiners with adjudication by a third reviewer in instances of disagreement. In our experience, there was a 74% agreement between the 2 initial reviewers with adjudication required in 26% of cases. In nearly all instances requiring adjudication, the disagreement was not related to whether fracture was present but rather qualifying the fracture severity (e.g., partial vs. complete).

Conclusions

Improvement of long-term restenosis-free patency with DES in TCOs has potentially significant clinical influence considering the persistently high rates of target lesion failure with bare-metal stents and the association of failure to achieve or sustain patency of TCOs with impairment in left ventricular function, recurrent angina, repeat target vessel revascularization, and a greater need for late bypass surgery (1). Further, the 4-fold reduction in failed patency with SES compared with bare-metal stents may conceivably influence clinical outcome given that patency is likely to be an even more important predictor of late clinical events than mere restenosis. For the period studied, treatment with SES as part of TCO revascularization appeared safe, with a low frequency of periprocedural myocardial infarction and no deaths. Although there were only 2 episodes of angiographically identified thrombosis (1 instance limited to a target vessel side branch outside of the stent itself), it is notable that these were observed against a background of high adherence (>80% at 1 year) to a dual antiplatelet regimen. Finally, stent fracture was not associated with stent thrombosis or aneurysm formation, and the site of stent fracture was uncommonly the culprit site of restenosis or TLR despite higher rates of repeat revascularization in this patient group. Dedicated long-term follow-up will further clarify the late safety and efficacy of DES treatment in this complex lesion subset, including the longer term impact of stent fractures. Even so, the results suggest that treatment with SES should be favored for percutaneous revascularization in chronically occluded native coronary arteries.

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Key Words: total coronary occlusion ■ sirolimus-eluting stent ■ drug-eluting stent ■ fracture.

APPENDIX

For a list of the ACROSS/TOSCA-4 trial study sites and principal investigators, please see the online version of this article.